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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/551,545

09/30/2005

Keiichi Miyamoto

Q90392

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23373 7590 05/11/2009
SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

EXAMINER

SYKES, ALTREV C

ART UNIT

PAPER NUMBER

1794

MAIL DATE

DELIVERY MODE

05/11/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/551,545	Applicant(s) MIYAMOTO ET AL.	
	Examiner ALTREV C. SYKES	Art Unit 1794	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 March 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12 is/are pending in the application.
- 4a) Of the above claim(s) 11 and 12 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 30 September 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Arguments

1. Applicant's arguments filed March 16, 2009 have been fully considered but they are not persuasive.

Applicant argues that Buscemi is silent as to a crosslinked elastin that exists in the gaps of the fibers. Applicant further argues that a crosslinking of elastin is not assumed in Buscemi and Buscemi does not have an intention of spoiling a drug by modification such as crosslinking. Applicant finally argues that Sasajima's crosslinked elastin used for reinforcing purposes is not applicable to the invention of Buscemi.

Examiner is not persuaded. Buscemi disclose the stent 10 includes a generally tubular main body 11 and a plurality of fibers 18 disposed around the main body 11. A plurality of apertures 14 extend through the stent 10. (See Figure 1 and Col 4, lines 15-20) Suitable biodegradable materials for the main body 11 of the stent 10 include polylactic acid, polyglycolic acid (PGA), collagen or other connective proteins or natural materials, polycaprolactone, hylauric acid, adhesive proteins, co-polymers of these materials as well as composites and combinations thereof and combinations of other biodegradable polymers. (See Col 6, lines 10-17) Buscemi et al. also discloses microcapsules may be included that induce crosslinking in the biodegradable material. The biodegradable material is then crosslinked and is strengthened. (See Col 9, lines 10-18) The stent also incorporates bioactive materials such as fibronectin, laminin, elastin, collagen, and integrins. (See Col 12, lines 47-49 and 59-60 and Col 13, lines 10-13) Therefore, examiner notes that the elastin in the stent would be crosslinked at the same

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time that the biodegradable material is crosslinked. The limitations as claimed by applicant for an elastin molded article are met by the stent as disclosed by Buscemi et al.

Regarding applicant's argument that the crosslinking would spoil the drug of Buscemi et al., examiner notes that applicant has provided no evidence to support this conclusion. The argument is further unpersuasive since Buscemi et al. discloses crosslinking of the stent materials.

Finally, with respect to the use of the crosslinked elastin of Sasajima, examiner maintains the position as set forth above. While Buscemi et al. discloses a crosslinked elastin, the reference is silent as to a *water-soluble* elastin. (*emphasis added*) However, examiner notes that since the crosslinked elastin of Buscemi et al. is to be used in a biodegradable stent for use in the human body, the elastin would naturally breakdown along with the rest of the stent materials by being dissolved in bodily fluids which would include water since it makes up 65% of the human body. Moreover, Sasajima et al. discloses an artificial blood vessel which has the elastin layer constructed for a bridge and formed of a crosslinking agent in water-soluble elastin thereby providing a strong anchoring effect to the structure. (See [0006] and [0007]) The elastin is further processed with enzymes to make it water soluble. (See [0009]) Therefore, examiner notes that it would have been obvious to one of ordinary skill in the art at the time of the invention motivated by expected success to utilize the enzyme processing as taught by Sasajima et al. for the crosslinked elastin of Buscemi et al. in order to provide a water-soluble elastin that would readily breakdown in the body.

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Applicant states in the remarks, the other cited references do not make up for this deficiency.

As examiner has clarified that no deficiency exists as set forth above, the position taken in the last mailed office action regarding the remaining references is maintained.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 1-7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buscemi et al. (US 5,500,013) in view of Sasajima et al. (JP 8-33661).

Regarding claims 1-3, Buscemi et al. discloses a molded stent including a main body of a generally tubular shape for insertion into a lumen of a vessel of a living being. (See Abstract) The rate of drug release is controlled by the rate of degradation of the biodegradable materials. (See Col 4, lines 11-14) The stent 10 includes a generally

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tubular main body 11 and a plurality of fibers 18 disposed around the main body 11. A plurality of apertures 14 extend through the stent 10. (See Figure 1 and Col 4, lines 15-20) Solid fibers, hollow fibers, or a combination thereof can be used. (See Col 4, lines 46-49) In one conventional method, solvation sealing, the steps of heat pressing and extrusion molding combine a film and fiber production into one step for the orientation of the polymer materials. (See Col 5, lines 1-14) Examiner equates extrusion molding of Buscemi et al. for the stent to the molded article of Applicant. Suitable biodegradable materials for the main body 11 of the stent 10 include polylactic acid, polyglycolic acid (PGA), collagen or other connective proteins or natural materials, polycaprolactone, hyaluric acid, adhesive proteins, co-polymers of these materials as well as composites and combinations thereof and combinations of other biodegradable polymers. (See Col 6, lines 10-17) Buscemi et al. also discloses microcapsules may be included that induce crosslinking in the biodegradable material. Once burst, the microcapsules release the materials that induce crosslinking of the biodegradable material. The biodegradable material is then crosslinked and is strengthened. (See Col 9, lines 10-18) The stent also incorporates bioactive materials such as fibronectin, laminin, elastin, collagen, and integrins. Fibronectin promotes adherence of the stent to the tissue of the vessel 12. (See Col 13, lines 10-13) Examiner therefore equates the stent as disclosed by Buscemi et al. to applicant's elastin molded article.

While Buscemi et al. discloses all of the claim limitations as set forth above, the reference does not specifically teach that the crosslinked water-soluble elastin or that the fiber diameter is 0.05 to 50 μ m.

Sasajima et al. discloses an artificial blood vessel capable of exhibiting high operability over a long period even with a small bore immobilizing elastin to the inside cavity surface of the vessel in such a manner that the elastin suppresses the clotting activity of blood on the material surface. (See Abstract) By forming a structure similar to the internal elastic membrane of a living body blood vessel in the inner surface of cavity of an artificial blood vessel in detail, the coagulation of blood and adhesion of a plasma protein are controlled. (See [0001]) Sasajima et al. discloses an artificial blood vessel which has the elastin layer constructed for a bridge and formed of a crosslinking agent in water-soluble elastin. (See [0006]) In order to fix collagen, elastin, etc. to an inner surface of cavity of an artificial blood vessel substrate produced tubular firmly, structure of an inner surface of cavity has porosity because the collagen or elastin would enter between a hole of a substrate providing a strong anchor effect to the structure. (See [0007]) Sasajima et al. also discloses it is appropriate for the fiber diameter to be in the range of 5-50 micrometers. (See [0008]) The elastin is further processed with enzymes to make it water soluble. (See [0009]) It is further possible to apply a solution of water-soluble elastin to construct a bridge in a cross linking agent, or to apply water-soluble elastin beforehand mixed with a cross linking agent and to construct a bridge by heating. (See [0015])

As Buscemi et al. and Sasajima et al. are both directed to vessels to be used in a living body, the art is analogous. Therefore, examiner notes that it would have been obvious to one of ordinary skill in the art at the time of the invention motivated by expected success to utilize the enzyme processing as taught by Sasajima et al. for the

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crosslinked elastin of Buscemi et al. in order to provide a water-soluble elastin that would readily breakdown in the body. It would have also been obvious to one of ordinary skill in the art at the time of the invention motivated by expected success to utilize fibers with a diameter in the range of 5-50 micrometers as taught by Sasajima et al. in order to provide for a structure similar to the internal elastic membrane of a living body blood vessel to better control the coagulation of blood and adhesion of plasma protein. (See [0001])

Regarding claim 4, Sasajima et al. discloses the elastin is further processed with enzymes to make it water soluble. (See [0009]) It is further possible to apply a solution of water-soluble elastin to construct a bridge in a cross linking agent, or to apply water-soluble elastin beforehand mixed with a cross linking agent and to construct a bridge by heating. (See [0015])

Regarding claims 6 and 7, Buscemi et al. discloses the stent also incorporates bioactive materials such as fibronectin, laminin, elastin, collagen, and integrins. Fibronectin promotes adherence of the stent to the tissue of the vessel. (See Col 13, lines 10-13) The bioactive materials are noted to be proteins.

Regarding claim 9, Buscemi et al. discloses the drugs or other biologically active materials incorporated into the stent perform a variety of functions. The functions include but are not limited to an anti-clotting or anti-platelet function; and preventing smooth muscle cell growth on the inner surface wall of the vessel. The drugs include but are not limited to drugs that inhibit or control the formation of thrombus or thrombolytics such as heparin or heparin fragments, carbohydrates, and proteins including but not limited to

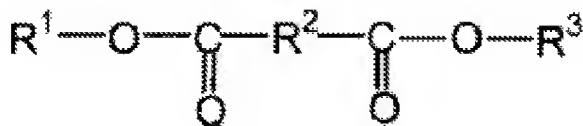
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antibodies (monoclonal and polyclonal) lymphokines and growth factors. (See Col 12, lines 59-67 and Col 13, lines 1-9)

5. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Buscemi et al. (US 5,500,013) in view of Sasajima et al. (JP 8-33661) as applied to claim 1 above, and further in view of Stedronsky et al. (US 6,033,654)

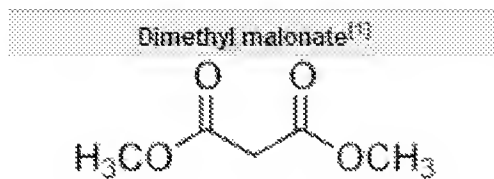
Regarding claim 5, Modified Buscemi et al. discloses all of the claim limitations as set forth above. Additionally, Sasajima et al. discloses although a glutaraldehyde which is a water-soluble cross linking agent, dialdehyde starch or a water-soluble epoxy compound, etc. can be used especially if it can react to an amino group and a functional group of both carboxyl groups. This construction gives a soft protein layer and is compliant with a living body blood vessel. (See [0016]) However, the reference fails to specifically disclose formula (1) as claimed by applicant shown below. Examiner notes that the formula (1) as presented by applicant is known generally as malonate.

Additionally, examiner finds evidence for such a conclusion via the internet article which references the Merck Index, 11th Edition (Centennial) published in November 1989. The second structure below provides a picture for comparison wherein the R¹ and R³ groups (in this case) are replaced with methyl groups (i.e. CH₃) making the structural name dimethyl malonate. The R² group is a CH₂ group.



Formula (1)

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It is noted by examiner that such a determination would have been well within the skill of one in the art at the time of the invention.

Further Stedronsky et al. discloses proteinaceous polymers having repetitive units from naturally occurring structural proteins are employed as backbones for functionalities for crosslinking to provide strongly adherent tissue adhesives and sealants. Particularly, block copolymers having repeating units of elastin and fibroin are employed having lysine substitutions in spaced apart units, where the amino group can be crosslinked using difunctional crosslinking agents. (See Abstract) A preferred adhesive composition may contain glutaraldehyde. Stedronsky et al. further discloses good mechanical and biological properties are exemplified by the strong adherent bonds to tissue. (See Col 2, lines 15-19, 30-40 and 51-57) Stedronsky et al. also discloses the crosslinking agent will normally be difunctional, where the functionalities may be the same or different, although higher functionality may be present, usually not exceeding four functionalities. (See Col 4, lines 4-7 and 13-22) The crosslinking agents will usually be at least about three carbon atoms and not more than about 50 carbon atoms, generally ranging from about 3 to 30 carbon atoms, more usually from about 3 to 16 carbon atoms. The chain joining the two functionalities will be at least one atom and not more than about 100 atoms, usually not more than about 60 atoms, preferably not more than about 40 atoms, particularly not more than about 20 atoms, where the atoms may be carbon, oxygen, nitrogen, sulfur,

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phosphorous, or the like. The linking group may be aliphatically saturated or unsaturated, preferably aliphatic, and may include such functionalities as oxy, ester, amide, thioether, amino, and phosphorous ester. The crosslinking group may be hydrophobic or hydrophilic. (See Col 4, lines 9-22) Stedronsky et al. discloses the crosslinking agents will usually be commercially available or may be readily synthesized in accordance with conventional ways, either prior to application of the adhesive or by synthesis in situ. (See Col 4, lines 42-45) Naturally occurring or synthetic bifunctional compounds may be employed. Illustrative compounds include di-(2'-aminoethyl) malonate, and the like. (See Col 5, lines 33-36) It is further noted by examiner that the use of malonate as a crosslinking agent is disclosed in the prior art. The two compositions may be dispensed simultaneously at the site of application. (See Col 5, lines 50-56) For example, the polyfunctional second compound may have amino and/or hydroxyl groups, where the protein has amino or hydroxyl functionalities. (See Col 5, lines 4-10) As such, it is noted by examiner that a crosslinking agent as claimed by applicant having the base of malonate would have been readily obvious using the disclosure of Stedronsky since the reference states that the crosslinking agent may have up to four functionalities which may include hydrophobic or hydrophilic properties, and include chains of up to 100 atoms which include sulfur and carbon. Stedronsky et al. discloses the subject compositions may find use in the formation of articles of manufacture, by themselves or in combination with other materials. The formed objects may be prepared in accordance with conventional ways, such as molding, extrusion, and the like. (See Col 7 lines 10-25) Additionally, it is noted that applicant describes in their provided disclosure the

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crosslinking agent having a hydrophobic portion in the center region of the molecule and having an amino group-reacting active ester group at both ends. (See [0018]) However, R_1 and R_3 can easily be chosen to include only carbon, sulfur, and hydrogen atoms which would eliminate an amino group-reacting active ester group for both ends since an amino group would need a nitrogen atom. As indicated by applicant's claim, R_4 and R_5 can both simply represent hydrogen. Additionally, R_2 can also be chosen to be $-(CH_2)_n-$ with n being 1. Finally, it is noted by examiner that the various substitutions provided for in the Stedronsky disclosure would only require routine experimentation for one skilled in the art motivated by the desire to acquire particular properties for the finally produced protein including water solubility.

As modified Buscemi et al. and Stedronsky et al. are both directed to molded articles containing crosslinking agents, the art is analogous. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to utilize the crosslinking agents as taught by Stedronsky et al. as the chosen water-soluble compound as disclosed by Sasajima for the added benefit of tailoring chemical or biological properties of interest with proteins utilized in biological systems. (See Col 4, lines 46-55) One of ordinary skill in the art would have recognized the available substitution of glutaraldehyde as disclosed by Sasajima with a crosslinking agent containing malonate as taught by Stedronsky.

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6. Claims 8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buscemi et al. (US 5,500,013) in view of Sasajima et al. (JP 8-33661) as applied to claim 1 above and further in view of Miyamoto (US 2004/0136977)

Regarding claims 8 and 10, modified Buscemi et al. discloses all of the claim limitations as set forth above. Buscemi et al. further discloses the drugs include but are not limited to drugs that inhibit or control the formation of thrombus or thrombolytics such as heparin or heparin fragments, carbohydrates, and proteins including but not limited to antibodies (monoclonal and polyclonal) lymphokines and growth factors. (See Col 12, lines 59-67 and Col 13, lines 1-9) However, the reference does not specifically disclose a polyamino acid is polylysine or a polyglutamic acid or that the cell growth factor is FGF.

Miyamoto ('977) discloses a crosslinked elastin comprising a crosslinking starting material containing at least one type of water-soluble elastin crosslinked with a water-soluble crosslinking agent. (See [0008]) The crosslinked elastin further comprises one or more components selected from among proteins such as collagen, gelatin, fibronectin, fibrin, laminin, casein, keratin, sericin and thrombin, polyamino acids such as polyglutamic acid and polylysine, cell growth factors such as bFGF (basic Fibroblast Growth Factor), TGF-.alpha. (Transforming Growth Factor .alpha.), EGF (Epidermal Growth Factor), VEGF (Vascular Endothelial Growth Factor) and CTNF (Ciliary NeuroTrophic Factor), as well as polycaprolactone, and polylactic acid. (See [0009])

As modified Buscemi et al. and Miyamoto ('977) are both directed to biocompatible material comprising crosslinking agents, the art is analogous. Therefore, it

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would have been obvious to one of ordinary skill in the art at the time of the invention to utilize the teaching of Miyamoto et al. to specifically choose the growth factor as discussed in the disclosure of Buscemi in order to provide any of a variety of additional functions to the stent. Also, it would have been well within the skill of one in the art to include the use of polyamino acids in the construction of the stent of Buscemi et al. since the disclosure of Miyamoto provides that polyamino acids are compatible with the combinations of drugs, bioactive materials, and other biologically active materials of Buscemi et al. and would not inhibit crosslinking. One would be motivated to do so in order to better tailor the final stent properties.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALTREV C. SYKES whose telephone number is (571)270-3162. The examiner can normally be reached on Monday-Thursday, 8AM-5PM EST, alt Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Tarazano can be reached on 571-272-1515. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/D. Lawrence Tarazano/

Supervisory Patent Examiner, Art Unit 1794

/ACS/

Examiner

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